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The prognostic significance of modified frailty index-5 in patients undergoing pneumonectomy for lung cancer

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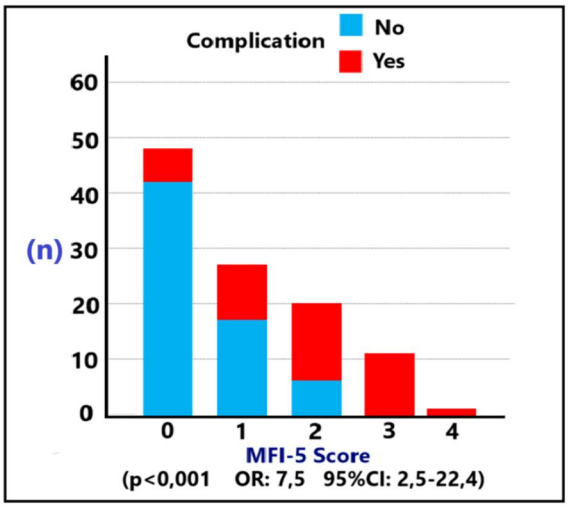
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Summary

The items of MFI-5 are DM, HT, COPD, CHF, and FS. We investigated effectivity of the MFI-5 score for predicting major postoperative complications in patients underwent pneumonectomy for NSCLC. A total of 107 patients were included in the study. Multivariate logistic regression analysis showed that >1 MFI-5 score is a significant indicator to predict major postoperative events



[**CHF:** Congestive Heart Failure, **COPD:** Chronic Obstructive Pulmonary Diseases, **DM:** Diabetes Mellitus, **FS:** Functionel Status, **MFI-5:** Modified Frailty Index-5, **NSCLC:** Non-Small Cell Lung Cancer]

Abstract

OBJECTIVES: In some centrally located lung cancers, complete excision of the mass cannot be achieved with parenchymal-sparing procedures and pneumonectomy may be required. The mortality and morbidity rates of pneumonectomy were reported to be considerably high. Here, we investigated the effectivity of modified frailty index-5 (MFI-5) in patients undergoing pneumonectomy for non-small cell lung cancer.

METHODS: Data of patients who underwent pneumonectomy for non-small cell lung cancer between January 2018 and December 2023 were reviewed retrospectively. The MFI-5 score was determined by preoperative diabetes mellitus, hypertension, chronic obstructive pulmonary diseases, congestive heart failure and functional status. The effectiveness of the MFI-5 score for the presence of

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postoperative major complications and 30-day mortality was investigated by multivariate logistic regression analysis. A P-value <0.05 was considered statistically significant.

RESULTS: A total of 107 patients who met the inclusion criteria were included in the study. Eight (7.5%) of patients were female, and the mean age was 61.4 ± 8.7. The MFI-5 score was 0 in 48 patients (44.9%), 1 in 27 patients (25.2%) and 2 in 20 patients (18.7%). Postoperative 30-day mortality was detected in 4 patients (3.7%), and the major complications occurred in 42 patients (39.3%). In multivariate analysis, an MFI-5 score of 2 or higher ($P = 0.008$, OR: 4.9) was statistically significant for complications, whereas age, gender, side of the operation, <2 MFI-5 score, tumor diameter, type of surgery and lymph node metastasis status were not statistically significant ($P > 0.05$).

CONCLUSIONS: The MFI-5 score is a significant indicator for predicting major postoperative events in patients who underwent pneumonectomy for non-small cell lung cancer.

Clinical registration number: 2024-323, approved by Gazi University Local Ethics Committee.

Keywords: Lung cancer • Modified frailty index-5 • Prognosis • Pneumonectomy

ABBREVIATIONS

CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
DM	Diabetes mellitus
MFI	Modified frailty index
NSCLC	Non-small cell lung cancer
TNM	Tumor Node Metastasis

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide, and histopathologically, the majority of cases are non-small cell lung cancer (NSCLC) [1]. In some centrally located lung cancers, complete excision of the mass cannot be achieved with parenchymal-sparing resections, and pneumonectomy may be required. Pneumonectomy is a procedure with very high morbidity and mortality, and studies have shown that especially right pneumonectomy is a disease in itself [2]. In the literature, several prognostic scores were defined for surgery patients. Frailty score was one of them and was 1st put forward at the beginning of the millennium by Fried *et al.* Frailty was defined as a biological syndrome associated with increased vulnerability to health stressors such as surgery [3]. When the frailty status of patients was 1st used for predicting postoperative complications, it included ∼70 items. Because of the difficulty of collecting and designing data in a multi-parameter scoring system, it was reduced to 11 factors and named modified frailty index (MFI)-11 and was shown to be able to replace the previous parameters. The number of items was further reduced by subsequent comparative studies, and the current MFI-5 criteria, which include diabetes, hypertension, heart failure, chronic obstructive pulmonary disease and functional status, were determined and were found effective in predicting postoperative complications. Reducing the items in frailty factors facilitated both data collection and analysis in the sequential studies [4–6].

Studies on diabetes mellitus (DM), which is one of the items of MFI-5, have shown that uncontrolled glucose levels increase postoperative complications. The negative effects of DM were especially emphasized on wound healing, infection and length of hospital stay in the studies. Additionally, surgical stress and some medications, such as corticosteroids, may dysregulate glycaemic control, and a vicious circle may occur [7, 8]. Both hypertension (HT) itself and the antihypertensives used can cause postoperative morbidity. Observational studies have reported that when major surgery is performed on patients who use angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for HT, the risk of fatal postoperative complications such as acute renal failure, acute coronary syndrome or stroke increases. The main reason for these events may be intraoperative sudden hypotension and perfusion problems after the anaesthesia induction [9]. HT also can cause cardiac instability and end-organ complications by vascular endothelial damage. In addition, comorbidities such as obesity, smoking, chronic kidney disease, carotid plaque, etc., which coexist with HT and are not included in MFI-5, may also cause increased postoperative complications and prolonged hospitalizations [10]. Chronic obstructive pulmonary disease (COPD) is an important cause of fatal postoperative pulmonary complications in non-thoracic surgical procedures and is even more important in pulmonary resections. Patients with COPD may be candidates for pneumonectomy for cure of NSCLC when their pulmonary capacity is adequate. Emphysematous individuals are vulnerable the postoperative pulmonary complications due to loss of pulmonary reserve, accompanying secondary pulmonary HT and failure of mucociliary clearance [11]. A significant increase in operative mortality as well as complications such as acute lung injury, bronchopleural fistula, prolonged air leak and atelectasis after pulmonary resection in patients with COPD were reported [12]. The relationship between congestive heart failure (CHF) and lung resection is bidirectional. While patients with CHF are vulnerable to postoperative morbidity and mortality after lung resection, major pulmonary resections may also cause cardiac instability. Preoperative cardiac evaluation before major pulmonary resection is very important, especially since the risk of cardiac complications can reach 15% after pneumonectomies. CHF is among the significant mortality indicators in the first 30 days after lung resection, especially in the elderly population [13, 14]. Functional status (FS) is a measure of a person's ability to independently perform daily activities such as eating, self-care or walking and is an umbrella factor that includes many comorbidities, such as advanced age, dementia, previous stroke, organ failure, etc. Although several scales are defined to evaluate the FS, roughly 2 scores are used in MFI-5 based on being able to perform all daily activities dependently or independently [15].

Though the effectivity of MFI-5 predicting postoperative complications in many surgical procedures is demonstrated, studies on pulmonary resections are scarce in the literature. To our knowledge, there is no report regarding MFI-5 in patients who underwent pneumonectomy for NSCLC. We aimed to investigate the effectivity of MFI-5 to predict major complications,

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including postoperative 30-day mortality, in patients who underwent pneumonectomy for NSCLC in this study.

MATERIALS AND METHODS

Patient selection

After the approval of the local ethics committee (approval number: 2024-323), data of patients who underwent pneumonectomy for lung cancer between January 2018 and December 2023 were reviewed retrospectively. Patients who operated for NSCLC were included in the study. Patients who underwent pneumonectomy for non-malignant diseases, such as bronchiectasis or destroyed lung, those with sarcoma, neuroendocrine tumours or metastatic diseases, those who underwent extrapleural pneumonectomy for malignant pleural mesothelioma and those whose medical records could not be reached were excluded. Figure 1 shows a CONSORT diagram of patient selection. The data collected were age, sex, side of surgery, type of surgery, tumour diameter, neoadjuvant therapy status, tumour stage, comorbidities of MFI-5, major postoperative complications and first 30-day mortality. Major complications were determined by higher than grade 2 according to the Clavien–Dindo classification [16].

Covariates

The criteria of major complications were determined as respiratory failure requiring intensive care and noninvasive/invasive mechanical ventilatory support or ECMO support, postoperative pneumonia in the contralateral lung, bleeding that requires surgery and/or causes signs of hypovolaemia, bronco-pleural fistula, postpneumonectomy empyema with or without fistula, acute renal failure needing haemodialysis, ischaemic or haemorrhagic stroke, cardiac events that cause haemodynamic instability, such as acute coroner syndrome or atrial/ventricular dysrhythmia, and postoperative death. Types of surgery were classified as standard, completion and extended pneumonectomy. Patients who had a history of ipsilateral pulmonary resection and required pneumonectomy due to tumour recurrence were included in the completed pneumonectomy group. Extended pneumonectomy criteria were intrapericardial pneumonectomy, carinal sleeve pneumonectomy, pneumonectomy with major vessel surgery, pneumonectomy with chest wall/diaphragm/left atrium/pericardium or vertebra resection. The items of MFI-5 were DM, HT, COPD, CHF and FS, and they were determined according to previous studies [4]. The HT score was marked as positive for patients who need antihypertensive medication. We considered patients' medical history and medications, signs of physical examination, values of pulmonary function tests and medical records of the Chest Diseases Consultant to make it positive for COPD score. The CHF score was based on the presence of heart failure confirmed by echocardiography or a Cardiology Consultant. FS score was determined as positive in patients who could not perform daily activities such as eating, walking, bathing etc. independently. FS refers to the ability to perform daily activities independently (self-care, showering, shaving, walking, etc.) due to mental status (dementia, stroke sequelae, etc.) or muscle weakness rather than a mechanical limitation such as an extremity fracture or absence of a limb.

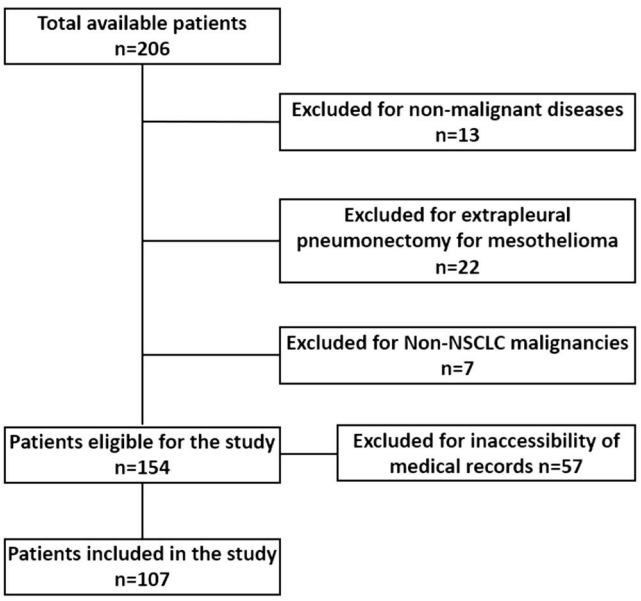


Figure 1: A CONSORT diagram of patient selection. NSCLC: non-small cell lung cancer.

Statistical analysis

All statistical analyses were performed by IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). The distribution normality of numerical variables was determined by histogram and Kolmogorov–Smirnov tests and given as mean with standard deviation or median with range according to normality. The categoric variables were given as *n* and percentage. The chi-square or Fisher's exact tests were used for categorical variables, and the Student-*t* test or Mann–Whitney *U*-tests were used for numerical variables to detect the correlation between complications and in univariate analyses. In the multivariate analysis, based on previous studies and univariate analysis results, age, operation side, gender, tumour diameter, type of surgery (standard, extended or completion), neoadjuvant therapy status, tumour stage and MFI-5 scores were determined as covariates. The patient's age is an important cause of complications. Decreased muscle strength with age, elastic recoil capacity of the lungs and multiorgan problems are predisposing factors for complications. In some studies, both postoperative complications and long-term survival in pulmonary resections were found to be worse in males [17, 18]. We added this variable to understand whether a gender effect exists. Studies have reported that right pneumonectomy has higher morbidity and mortality rates than left pneumonectomy [19]. Therefore, we aimed to investigate the effect of the operation side by multivariate analysis. Although all patients underwent pneumonectomy, we included variables such as tumour size, extended resection (pericardial or diaphragmatic resection), neoadjuvant treatment status and reoperation status in the multiple analysis because they may affect the postoperative complication rate. To avoid the effect of multicollinearity, multivariate analyses were performed separately for MFI-5 scores 1 and 2. Additionally, the components of MFI-5 were not included in the analysis as a covariate. Analyses

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were performed with a 95% confidence interval. A *P*-value of <0.05 was considered statistically significant.

RESULTS

A total of 107 patients who met the inclusion criteria were included in the study. Eight (7.5%) of patients were female, and the mean age was 61.4 ± 8.7. The number and rate of right and left pneumonectomies were 40 (37.4%) and 67 (62.6%), respectively. The median tumour diameter was 5cm (range: 1–13.9 cm). Twenty of the patients (18.6%) received neoadjuvant treatment. The most common tumour stage, according to the 8th Tumour Node Metastasis (TNM) system, was II in 42 patients (39.3%). Forty-eight of patients (44.9%) had no preoperative comorbidity, and their MFI-5 score was zero. The most common comorbidity was HT in 36 patients (33.6%). The major complications were detected in 42 patients (39.3%) according to the Clavien–Dindo classification, and the most common problems were empyema and bleeding in 11 patients (10.2%). The readmission rate was 5.6% (in 6 patients). The demographic data are given in Table 1. There was a significant correlation between age ($P = 0.04$, odds ratio: 1.05), 2 and higher MFI-5 scores ($P < 0.001$, odds ratio: 7.5) and postoperative complications in univariate analyses. The

Table 1: Patient's demographics, $n = 107$

			n	%
Age (year), mean ± SD	61.4 ± 8.7			
Tumour diameter (cm), median (range)	5 (1–13.9)			
Gender	Female		8	7.5
	Male		99	92.5
Side	Right		40	37.4
	Left		67	62.6
N status	N0		47	43.9
	N1		35	32.7
	N2		25	23.4
Hypertension	Yes		36	33.6
	No		71	66.4
CHF	Yes		8	7.5
	No		99	92.5
COPD	Yes		23	21.5
	No		84	78.5
Functional status	Dependent		11	10.3
	Independent		96	89.7
Diabetes mellitus	Yes		28	26.2
	No		79	73.8
Major complications	Yes[a]		42	39.3
		ARF	2	1.8
		Bleeding	11	10.2
		BPF	8	7.5
		Death	4	3.7
		Dysrhythmia	5	4.7
		Empyema	11	10.2
		Liver dysfunction	1	0.9
		Pneumonia	6	5.6
		Respiratory failure	8	7.5
		Revision surgery	9	88
		Stroke	3	2.8
	No		65	60.7
Type of surgery	Standard Pn.		91	85.0
	Completion Pn.		3	2.8
	Extended Pn.		13	12.1
Tumour stage (8^{th} TNM)	IA		9	8.4
	IB		13	12.1
	II		42	39.3
	IIIA		35	32.7
	IIIB		8	7.5
Neoadjuvant treatment	Yes		20	18.7
	No		87	81.3
MFI-5 score	0		48	44.9
	1		27	25.2
	2		20	18.7
	3		11	10.3
	4		1	0.9
	5		0	0

ARF: acute renal failure; BPF: broncho-pleural fistula; CHF: congestive heart failure; COPD: chronic obstructive pulmonary diseases; MFI-5: modified frailty index-5; *N*: mediastinal lymph node; Pn: pneumonectomy; SD: standard deviation; TNM: Tumor Node Metastasis.

[a]Some patients may have more than 1 complication.

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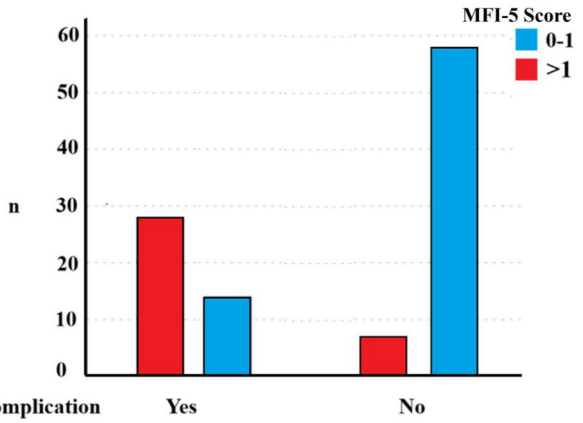


Figure 2: The figure shows a significant correlation between high MFI-5 scores and postoperative complications. MFI-5: modified frailty index-5.

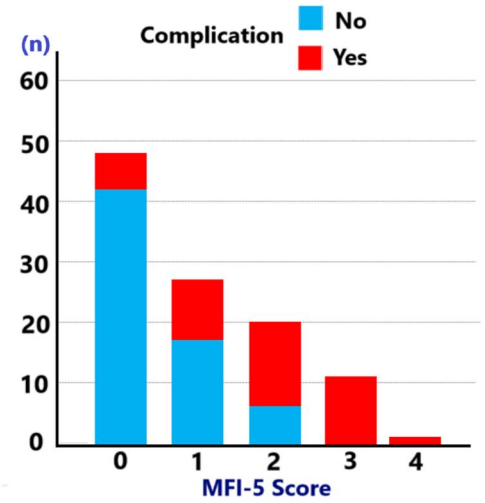


Figure 3: The figure shows the complication rates according to the MFI-5 score. MFI-5: modified frailty index-5.

Table 2: Results of univariate and multivariate analysis according to some covariates

	Univariate			Multivariate		
Covariates	*P*-value	OR	95% CI	*P*-value	OR	95% CI
Age	0.04	1.05	1.0–1.1	0.08	1.05	0.8–1.2
Side	0.07	2.1	0.9–4.7	0.1	2.3	0.8–6.4
Gender	0.9	1.05	0.2–4.6	0.8	0.6	0.04–9.2
Tumor diameter	0.7	1.01	0.8–1.1	0.8	1.03	0.8–6.4
Type of surgery	0.09	1.6	0.8–3.2	0.3	2.2	0.2–3.1
Neoadjuvant therapy	0.8	0.9	0.3–2.5	0.9	1.1	0.1–6.5
Tumor stage	0.3	1.4	0.6–3.2	0.2	2.3	0.4–11.3
MFI-5 score 1 vs 0	0.09	3.1	0.8–10.5	0.1	2.8	0.6–12.4
MFI-5 score ≥ 2 vs 0	<0.001	7.5	2.5–22.4	0.008	4.9	1.5–16.2

CI: confidence interval; MFI-5: modified frailty index-5; OR: odds ratio.

multivariate logistic regression analyses showed the only significant factor for postoperative complications was ≥2 MFI-5 score (*P*: 0.008, odds ratio: 4.9, 95% confidence interval: 1.5–16.2, Fig. 2, Table 2). In the comparative tables, complications were detected in only 6 (12.5%) of the patients with an MFI-5 score of 0, while the complication rate in patients with scores of 1, 2 and 3 was 37%, 70% and 100%, respectively (Fig. 3, Table 3).

DISCUSSION

This study demonstrated that ≥2 MFI-5 score significantly predicted postoperative major complications, including death in patients who underwent pneumonectomy for NSCLC. The MFI-5 score has been shown to be very effective in predicting postoperative events in various types of malignancies and has been used as part of the 'National Surgical Quality Improvement Program' in some countries. A prospective study including 259 gynaecological malignancies conducted by Mah *et al.* [20] concluded that both surgical complication rates and adverse chemotherapy outcomes were significantly higher in patients with an MFI-5 score of 2 or more. Ogata *et al.* [21] reported in a retrospective study including patients with colorectal carcinoma that the postoperative mortality was significantly higher in patients with an MFI-5 score of 3 and above, and the complication rate was no different. There are very few studies investigating the relationship between lung cancer and MFI-5 in the literature. Franco *et al.* [22] reported that 3-year overall survival and non-cancer mortality were significantly worse in the group with ≥2 MFI-5 score in elderly patients with NSCLC treated by radiotherapy. In a database study with a very large cohort, including patients who underwent anatomical resection, Lee and Ferguson [23] found a significant increase in the risk of almost all postoperative complications, except cardiovascular complications, in all MFI-5 scores. Moreover, they reported that the presence of general major complications occurs at ≥2 MFI-5 score, and the risk of postoperative death occurs at ≥3 MFI-5 score. Although we could not perform analyses separately for each complication due to the limited number of patients in our study, similarly, we detected ≥2 MFI-5 score could predict major postoperative events. Wada *et al.* [4] showed that the risk of postoperative complications increased significantly in patients who had ≥2 MFI-5 score and detected that the most common complication was pulmonary complications in their study involving patients who underwent pulmonary lobectomy for NSCLC. Although the results of our study were similar in terms of MFI-5 score, the most common complication in our study was empyema and bleeding. The reason for this may be that the patients included in our study were patients who underwent pneumonectomy, that is, a more major operation than other pulmonary resections. Tamburini *et al.* [24] demonstrated that the readmission and postoperative complication rates were significantly higher in the group with a high frailty index in a study including patients who underwent pulmonary resections for lung cancer, and they reported that the common reasons for readmission were pulmonary and cardiac complications. Our readmission rate was 5.6%; underlying factors were similar.

Our study had several limitations. The first of these is the natural limitations of its being a retrospective and single-centre feature. Another limitation was the small number of patients in the cohort. For this reason, we could not analyse separately for frailty factors and postoperative complications. Another

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Table 3: Crosstabs of major complications and some covariates

		Total *n*	Major complication: yes	Major complication: no
MFI-5 score	0	48	6 (12.5 %)	42 (85.5%)
	1	27	10 (37 %)	17 (63%)
	2	20	14 (70%)	6 (30%)
	3	11	11 (100%)	–
	4	1	1 (100%)	–
	5	–	–	–
Hypertension	Yes	36	24 (66.6%)	12 (33.4%)
	No	71	18 (25.3%)	53 (74.7%)
DM	Yes	28	20 (71.4%)	8 (28.6%)
	No	79	22 (27.9%)	57 (72.1%)
COPD	Yes	23	14 (60.9%)	9 (39.1%)
	No	84	28 (33.3%)	56 (66.7%)
CHF	Yes	8	7 (87.5%)	1 (12.5%)
	No	99	35 (35.3%)	64 (64.7%)
Functional status	Dependent	11	10 (90.9%)	1 (9.1%)
	Independent	96	32 (33.3%)	65 (67.7%)
Type of surgery	Standard Pn	91	37 (40.6%)	54 (59.4)
	Completion Pn.	3	2 (66.7%)	1 (33.3)
	Extended Pn.	13	3 (23 %)	10 (77%)
N status	N0	47	19 (40.4%)	28 (59.6%)
	N1	35	15 (42.8%)	20 (58.2%)
	N2	25	8 (32%)	17 (68%)
Age	<65	71	33 (46.4%)	38 (53.6%)
	≥65	36	9 (25%)	27 (75%)

CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; MFI-5: modified frailty index 5; *N*: lymph node metastasis; Pn: pneumonectomy.

limitation was that we could not analyse the MFI-5 score predicting the postoperative 30-day mortality and readmission rates due to their low number. Another limitation of our study is that a good quality long-term overall survival analysis could not be performed because the study's end date was December 2023. Another issue that could be considered as a limitation was that gender-based analysis was not optimal because the number of female patients included in our study was very small. An important limitation was that due to the small number of patients, no correlation could be made between the degree of comorbidity and complications; only the presence or absence of the MFI-5 item was considered.

As a result, a high MFI-5 score is significantly associated with postoperative major complications in patients who underwent pneumonectomy with the diagnosis of NSCLC. The high rate of postoperative complications should be considered, especially in patients with dependent FS and DM. Our results need to be supported by multicentre prospective studies.

FUNDING

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Conflict of interest: All authors declare there is no conflict of interest.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Muhammet Sayan: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **Bengisu Artiran:** Conceptualization; Data curation; Supervision; Visualization; Writing—original draft. **Funda Ozturk:** Conceptualization; Data curation; Supervision; Visualization; Writing—original draft; Writing—review & editing. **Mahir Fattahov:** Conceptualization; Investigation; Supervision; Writing—original draft. **Irmak Akarsu:** Conceptualization; Data curation; Supervision; Visualization; Writing—original draft; Writing—review & editing. **Muhammet Tarik Aslan:** Conceptualization; Data curation; Formal analysis; Supervision; Visualization; Writing—original draft. **Gunel Ahmadova:** Conceptualization; Data curation; Investigation; Supervision; Visualization; Writing—original draft. **Aysegul Kurtoglu:** Conceptualization; Data curation; Formal analysis; Investigation; Supervision; Writing—original draft. **Ismail Cuneyt Kurul:** Conceptualization; Data curation; Methodology; Validation; Visualization; Writing—original draft; Writing—review & editing. **Ali Celik:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

Reviewer information

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